OBSTETRICS

Risk of placental dysfunction disorders after prior miscarriages: a population-based study

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OBJECTIVE: The objective of the investigation was to study the association between prior miscarriages and the risks of placental dysfunction disorders, including preeclampsia, stillbirth, birth of a small for gestational age (SGA) infant, placental abruption, and spontaneous preterm birth.

STUDY DESIGN: In a population-based cohort study including 619,587 primiparous women, we estimated risks of placental dysfunction disorders for women with 1 (n = 68,185), 2 (n = 11,410) and 3 or more (n = 3823) self-reported prior miscarriages. Risks were calculated as odds ratios by unconditional logistic regression analysis and adjustments were made for maternal age, early pregnancy body mass index, height, smoking habits, country of birth, years of formal education, in vitro fertilization, chronic hypertension, pregestational diabetes, hypothyroidism, systemic lupus erythematosis, fetal sex, and year of childbirth.

RESULTS: Compared with women with no prior miscarriage, women with 1 prior miscarriage had almost no increased risks. Women with 2 prior miscarriages had increased risks of spontaneous preterm birth, preterm (<37 weeks) SGA infant, and placental abruption. The rates of all disorders were higher for women with 3 or more prior miscarriages compared with women without prior miscarriages: preeclampsia, 5.83% vs 4.27%; stillbirth, 0.69% vs 0.33%, SGA infant, 5.09% vs 3.22%, placental abruption, 0.81% vs 0.41%; and spontaneous preterm birth, 6.45% vs 4.40%. The adjusted odds ratios for preterm (<37 weeks) disorders in women with 3 prior miscarriages were approximately 2.

CONCLUSION: History of 2 or more miscarriages is associated with an increased risk of placental dysfunction disorders and should be regarded as a risk factor in antenatal care.

Key words: intrauterine growth restriction, miscarriage, placental abruption, preeclampsia, spontaneous preterm birth, stillbirth

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Failure of implantation has been suggested to be involved not only in the pathogenesis of miscarriage but also in pregnancy complications associated with placental dysfunction (ie, preeclampsia, stillbirth, intrauterine growth restriction, placental abruption, and spontaneous preterm birth).[1-3] Implantation and placentation can be presented as a continuous process regulated by complex signaling between decidua, immune cells, and fetal tissue.[3]

Vascular adaptation of the uterus, including angiogenesis and spiral artery remodeling, is a key feature in early placental development.[4] Former studies have shown that both miscarriage and placental dysfunction disorders are associated with an imbalance in angiogenic activity, disturbances in uterine blood supply, and placental oxidative stress.[4-7] It has been hypothesized that a complete implantation/placentation failure may result in a miscarriage, whereas a partial failure may result in late pregnancy complications associated with placental dysfunction.[5,8]

Based on the similarities in pathogenesis of miscarriage and placental dysfunction disorders, a history of prior miscarriages might be associated with increased risk of placental dysfunction disorders. This hypothesis is supported by a few previous studies, in which the exposure was either miscarriage or in vitro fertilization (IVF).[9-14] In some of these studies, parity was not controlled for,[10-12] or primiparous women exposed for prior miscarriages were compared with parous women.[13,14] Comparing primiparous women with prior miscarriages with a reference group of parous women might overestimate risks because placental dysfunction disorders are more prevalent in primiparous compared with parous women.[15]

In this study we had the opportunity to obtain data on the number of prior miscarriages and pregnancy complications from more than 600,000

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primiparous women. We hypothesized the following: (1) there is an association between prior miscarriage and the placental dysfunction disorders preeclampsia, stillbirth, intrauterine growth restriction, placental abruption, and spontaneous preterm birth in primiparous women; (2) the strength of the association increases by the number of previous miscarriages; and (3) risks are higher in preterm (<37 weeks) than in term placental dysfunction disorders (≥37 weeks) because preterm disorders are stronger related to placentation failure than term disorders.[16,17]

Materials and Methods

The Swedish Medical Birth Register contains data on more than 98% of all births in Sweden since 1973,[18] including demographic data, information on reproductive history and complications during pregnancy, delivery, and the neonatal period. In Sweden antenatal care is standardized and free of charge. During the first antenatal visit, usually taking place at the end of the first trimester,[19] the mother is interviewed about her medical and obstetric history. Information about maternal characteristics such as weight, height, and smoking habits are also recorded.

After delivery, the responsible doctor records women's diseases and complications during pregnancy and delivery, according to the *International Classification of Diseases* (ICD). Information about pregnancy and delivery is forwarded to the Birth Register through copies of standardized antenatal, obstetric, and pediatric records. Individual record linkage between the Birth Register and other registries is possible through each individual's unique personal registration number, assigned to each Swedish resident.[20]

Study population and exposure variable

Women giving birth to their first singleton infant at 22 weeks of gestation or later during the period 1995-2009 (n = 619,587) were included. Exposure variable was number of self-reported prior miscarriages, recorded by the midwife at the first antenatal visit. Number of miscarriages was categorized into no prior miscarriage (n = 536,169), 1 miscarriage (n = 68,185), 2 miscarriages (n = 11,410), and 3 or more miscarriages (n = 3,823).

Outcomes

Placental dysfunction disorders included preeclampsia, stillbirth, intrauterine growth restriction, placental abruption, and spontaneous preterm birth.

Preeclampsia was defined through the ICD-9 and ICD-10 codes 642E-G and O14-O15. The clinical definition of preeclampsia during the study period was a rise in blood pressure (≥140/90 mm Hg) combined with proteinuria (≥0.3 g/24 hours or +1 or more on dipstick on at least 2 occasions). The quality of the diagnosis of preeclampsia has been validated previously: of 148 pregnancies coded as preeclampsia in the Birth Register, 137 (93%) had the disease according to the individual records.[21] During most of the study period (before July 1, 2008), stillbirth was defined as fetal death at 28 weeks of gestation or later. Analysis of stillbirth was therefore restricted to births at 28 weeks or later. The total population when calculating risk of stillbirth included 617,708 births.

Being born small for gestational age (SGA) was used as a proxy for intrauterine growth restriction. SGA was defined as a birthweight below 2 SD from the mean birthweight for gestational age, according to the sex-specific Swedish fetal growth curve.[22] Only live births were included in this analysis, and pregnancies with missing information on infant's birthweight were excluded (n = 2252). The total population when calculating risk of SGA included 615,130 births. Placental abruption was defined through ICD-9 and ICD-10 codes 641C and O45.

Preeclampsia, stillbirth, birth of an SGA infant, and placental abruption were categorized into preterm (birth before 37 weeks of gestation) and term (birth at 37th week of gestation or later). In Sweden, gestational age is assessed by ultrasound scans in 97% of women, usually around the 17th week of gestation.[23] If no early second-trimester ultrasound scan was available, the last menstrual period was used to calculate gestational age at delivery.

Spontaneous preterm birth was defined as a birth before 37 gestational weeks with a spontaneous onset. At delivery, the responsible midwife records start of labor using the check boxes; spontaneous labor, induced or caesarean section. A total of 6720 births had no information on labor onset and were excluded from this analysis. All births with a diagnosis of preterm premature rupture of the membranes (ICD-9 and ICD-10 codes 658B and O42) were defined as a spontaneous onset in the study. Spontaneous preterm births were categorized into very preterm births (birth before 32 weeks of gestation) and moderately preterm births (birth from 32 to 36 full weeks of gestation). The birth of an SGA infant was excluded from the analysis. The total population when calculating the risk of spontaneous preterm births included 596,659 births.

Covariates

Information about maternal age and fetal sex was collected at delivery, whereas information about body mass index (BMI), height, smoking habits, cohabitation with infant's father, and IVF was collected from the first antenatal visit. The variables were categorized according to Table 1. To achieve information on the mothers' country of birth and highest level of formal education, individual linkages with the Register of Total Population and the Education Register (Dec. 31, 2010) were performed. The mother's country of birth was categorized to Nordic (Denmark, Finland, Iceland, Norway, and Sweden) and non-Nordic countries, and years of formal education were categorized into 3 levels according to Table 1.

Women with chronic hypertension, pregestational diabetes, hypothyroidism, or systemic lupus erythematosis (SLE) were identified with check boxes from the first antenatal visit and/or diagnostic codes from hospital discharge: chronic hypertension (check box; ICD-9 codes 642A-C; ICD-10 codes O10-11 and I10-15), pregestational diabetes (check box; ICD-9 codes 648A and 250; ICD-10 codes E10-E14 and O240-O243),

hypothyroidism (ICD-9 code 244 and ICD-10 code E03), and SLE (check box; ICD-9 code 710A and ICD-10 code M32).

Statistical methods

The associations between 1, 2, and 3 or more prior miscarriages on the risks of preeclampsia, stillbirth, SGA birth, placental abruption, and spontaneous preterm birth were estimated in primiparous women, using women with no prior miscarriage as reference. Odds ratios with 95% confidence intervals were calculated by unconditional logistic regression analysis with adjustments for maternal and infant characteristics. The following variables were initially included in our multiple logistic regression model: maternal age, early pregnancy BMI, height, smoking habits, cohabitation with infant's father, mother's country of birth, years of formal education, IVF, chronic hypertension, pregestational diabetes, hypothyroidism, SLE, fetal sex, and year of birth (categorized into years 1995-1999, 2000-2004, and 2005-2009). Cohabitation with infant's father did not influence any of our outcomes and was therefore excluded from the final model.

Because the causes of miscarriages may vary with maternal age,[24,25] we considered that age might modify the effect of miscarriages on the outcomes. Effect measure modification was investigated by introducing cross-product terms between number of miscarriages and maternal age as categorical variables in the regression models of each outcome; a value of $P < .05$ was considered significant. There was no effect measure modification between the number of prior miscarriages and maternal age concerning the outcomes: preeclampsia, $P = .24$; stillbirth, $P = .41$; SGA, $P = .08$; placental abruption, $P = .12$; or spontaneous preterm birth, $P = .84$. All analyses were performed using the Statistical Analysis Software version 9.2 (SAS Institute, Inc, Cary, NC).

Details of ethics approval

The study was approved by one of the regional ethical review boards in

TABLE 1
Number of prior miscarriages by maternal characteristics

Maternal characteristic	n	Prior miscarriages 0, %	1, %	2, %	≥3, %
Age, y					
<25	159,004	26.6	21.6	16.6	12.8
25-29	230,568	38.0	34.0	29.6	24.6
30-34	168,425	26.8	30.0	32.0	33.7
≥35	60,000	8.7	14.5	21.8	29.0
Data missing	1590				
BMI, kg/m^2					
<18.5	15,843	3.0	2.6	2.5	1.5
18.5-24.9	356,391	66.9	63.8	60.3	59.2
25.0-29.9	119,136	21.9	23.7	25.8	25.6
≥30.0	45,472	8.2	9.9	11.3	13.7
Data missing	82,745				
Height, cm					
<162	120,680	21.0	21.2	21.5	22.7
162-171	325,780	56.9	56.7	57.0	56.0
≥172	126,360	22.1	22.1	21.5	21.3
Data missing	46,767				
Smoking (cigarettes/d)					
0	524,055	90.3	88.3	87.8	86.8
1-9	44,546	7.5	8.9	9.0	8.9
≥10	13,396	2.2	2.8	3.1	4.3
Data missing	37,590				
Mothers' country of birth					
Nordic	518,084	84.8	85.3	85.1	86.1
Non-Nordic	92,103	15.2	14.7	14.9	13.9
Data missing	9400				
Education, y					
≤9	48,601	8.0	8.8	9.4	10.3
10-14	341,539	57.1	58.2	58.1	58.2
≥15	206,798	34.9	33.0	32.5	31.4
Data missing	22,649				
IVF					
No	603,754	97.7	96.0	94.1	92.5
Yes	15,833	2.3	4.0	5.9	7.5
Chronic hypertension					
No	616,243	99.5	99.4	99.2	99.1
Yes	3344	0.5	0.6	0.8	0.9

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TABLE 1
Number of prior miscarriages by maternal characteristics *(continued)*

Maternal characteristic	n	Prior miscarriages 0, %	1, %	2, %	≥3, %
Pregestational diabetes					
No	616,281	99.5	99.4	99.1	99.1
Yes	3306	0.5	0.6	0.9	0.9
Hypothyroidism					
No	617,460	99.7	99.6	99.4	99.0
Yes	2127	0.3	0.4	0.6	1.0
SLE					
No	619,027	99.9	99.9	99.9	99.6
Yes	560	0.1	0.1	0.1	0.4
Fetal sex					
Male	318,748	51.5	51.3	51.0	51.7
Female	300,716	48.5	48.7	49.0	48.3
Missing	123				
Total	619,587	536,169	68,185	11,410	3823

BMI, body mass index; *IVF*, in vitro fertilization; *SLE*, systemic lupus erythematosis.

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Stockholm, Sweden. The reference number was 2012/2088-32.

RESULTS

Compared with women with no prior miscarriage, women with prior miscarriages were older, had a higher BMI, and were more often smokers. Furthermore, women with prior miscarriages were slightly more often born in a Nordic country, had shorter formal education, were more often pregnant after IVF treatment, and were more likely to have chronic hypertension, pregestational diabetes, hypothyroidism, and SLE (Table 1).

Preeclampsia and stillbirth

Compared with women with no prior miscarriage, women with 1 or 2 prior miscarriages did not have increased risks of preeclampsia or stillbirth. The rates of preeclampsia and stillbirth were higher in women with 3 or more prior miscarriages than in women without prior miscarriage: 5.83% vs 4.27% and 0.69% vs 0.33%, respectively. When we divided the outcomes into preterm and term disorders, the associations were significant only between 3 or more miscarriages and preterm disorders (Table 2).

Small for gestational age and placental abruption

Compared with women with no prior miscarriage, women with 1 prior miscarriage did not have increased risks of SGA or placental abruption. Women with 2 prior miscarriages had slightly increased risks of preterm SGA infant and placental abruption. The rates of an SGA infant and placental abruption were higher in women with 3 or more prior miscarriages than in women without prior miscarriage: 5.09% vs 3.22% and 0.81% vs 0.41%, respectively. The adjusted ORs for preterm SGA and placental abruption in women with 3 prior miscarriages were around 2 (Table 3).

Spontaneous preterm births

Compared with women with no prior miscarriage, women with prior miscarriages had an increased risk of spontaneous preterm birth and the risk showed a dose-response pattern. The rates of spontaneous preterm births for women with no prior miscarriage, 1, 2, and 3 or more prior miscarriages were 4.40%, 4.46%, 5.05%, and 6.45%, respectively. The association seemed strongest between 3 or more prior miscarriages and very preterm (birth before 32 weeks) births, with adjusted odds ratio, 2.60 (95% confidence interval, 1.86–3.64) (Table 4).

COMMENT

Main findings

In this large population-based study of primiparous women, we showed that prior miscarriages were associated with increased risks of the placental dysfunction disorders preeclampsia, stillbirth, SGA birth, placental abruption, and spontaneous preterm birth. The associations were strongest for 3 or more prior miscarriages and seemed stronger for preterm placental dysfunction disorders compared with term disorders. The results support the notion that miscarriages and placental dysfunction disorders might partially share the same pathogenesis.

Strengths and limitations

The major strength of our study was the large study population. This enabled us to stratify the exposure by number of miscarriages and also to study rare events like stillbirth and placental abruption and to subdivide these outcomes into preterm and term disorders. Another strength was the population-based design, suggesting that the results from this national study are generalizable to other settings. In contrast to some previous studies,[10,11,13] we were able to control for important confounders such as maternal smoking, BMI, and IVF as well as chronic hypertension, pregestational diabetes, hypothyroidism, and SLE. However, we had no information about other potential confounders, including thrombophilia and polycystic ovarian syndrome.[26,27] Exposure was measured as self-reported miscarriages, which might be both a strength and limitation. Self-reported information made it possible to include miscarriages experienced by the women regardless of a need for specialist care. However, we had no information about their underlying etiology or gestational length at

miscarriage. Another potential limitation is lack of data on prior induced abortions. In a recent review, induced abortions were associated with increased risks of placental abruption and low birthweight but a reduced risk of preeclampsia.[28]

Interpretation

A dose-response relationship was previously shown between prior miscarriages and spontaneous preterm birth, which is in agreement with our finding.[29,30] Regarding other outcomes, there are to our knowledge only 3 previous studies on the association between miscarriages and placental dysfunction disorders, including solely primiparous women in both the exposed and the reference group. Two of these studies investigated the effect of less than three prior miscarriages on preeclampsia or intrauterine growth restriction.[13,14] These results are in agreement with our findings, showing limited effect on the outcomes. The third study investigated the effect of 3 or more miscarriages on preeclampsia.[9] This study could not report a significant increased risk of preeclampsia, which may have been due to lack of power because the sample size of women with 3 or more miscarriages was only 130.

The results in this study are in accordance with the hypothesis that miscarriage and placental dysfunction disorders have a partially common pathogenesis of early placentation failure.[8] Vascularization of the endometrium is of main importance for successful implantation and placentation.[31] Vascular endothelial growth factor (VEGF) is an important proangiogenic factor,[32] and increased expression of VEGF in first-trimester decidua has been associated with both miscarriage and placental dysfunction disorders.[4,33] Increased angiogenic activity and a premature onset of the maternal circulation in early placental development could result in subsequent increase in oxidative stress.

It has been hypothesized that if these disturbances are severe, this may lead to a complete failure of early placentation and miscarriage.[6,33] However, if the failure is partial, the pregnancy might

TABLE 2
Risks of preeclampsia and stillbirth by number of prior miscarriages

Prior miscarriages	Preeclampsia total			Preterm preeclampsia			Term preeclampsia			Stillbirth[b] total			Preterm stillbirth[b]			Term stillbirth[b]		
	n	Rate, %	AOR[a] (95% CI)	n	Rate, %	AOR[a] (95% CI)	n	Rate, %	AOR[a] (95% CI)	n	Rate, %	AOR[a] (95% CI)	n	Rate, %	AOR[a] (95% CI)	n	Rate, %	AOR[a] (95% CI)
No	22,915	4.27	1.00	5095	0.95	1.00	17,820	3.32	1.00	1790	0.33	1.00	773	0.14	1.00	1017	0.19	1.00
Yes																		
1	2989	4.38	0.98 (0.94–1.02)	665	0.98	1.00 (0.92–1.09)	2324	3.41	0.98 (0.94–1.03)	238	0.35	0.96 (0.83–1.12)	97	0.14	0.95 (0.75–1.21)	141	0.21	0.98 (0.80–1.19)
2	501	4.39	0.94 (0.85–1.04)	123	1.08	1.07 (0.88–1.30)	378	3.31	0.92 (0.82–1.03)	41	0.36	1.02 (0.73–1.42)	14	0.12	0.94 (0.54–1.63)	27	0.24	1.08 (0.71–1.64)
≥3	223	5.83	1.23 (1.06–1.42)	67	1.75	1.62 (1.24–2.11)	156	4.08	1.17 (0.98–1.38)	26	0.69	1.62 (1.05–2.51)	14	0.37	2.25 (1.23–4.10)	12	0.32	1.29 (0.69–2.42)

AOR, adjusted odds ratio; *CI*, confidence interval.

[a] Adjustments were made for maternal age, body mass index, height, smoking, country of birth, years of formal education, in vitro fertilization, chronic hypertension, pregestational diabetes, hypothyroidism, systemic lupus erythematosis, fetal sex, and year of birth;
[b] Infants at least 28 weeks of gestation included in the analysis. Total population n = 617,708.

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TABLE 3
Risks of SGA and placental abruption by number of prior miscarriages

	SGA[a] total			Preterm SGA[a]			Term SGA[a]		
Prior miscarriages	n	Rate, %	AOR (95% CI)[b]	n	Rate, %	AOR (95% CI)[b]	n	Rate, %	AOR (95% CI)[b]
No	17,119	3.22	1.00	3468	0.65	1.00	13,651	2.56	1.00
Yes									
1	2241	3.31	0.98 (0.93–1.03)	504	0.74	1.08 (0.97–1.20)	1737	2.57	0.96 (0.91–1.01)
2	424	3.75	1.06 (0.95–1.18)	113	1.00	1.32 (1.07–1.62)	311	2.75	1.01 (0.89–1.14)
≥3	192	5.09	1.38 (1.18–1.62)	68	1.80	2.21 (1.69–2.88)	124	3.29	1.20 (0.99–1.46)
	Placental abruption total			**Preterm placental abruption**			**Term placental abruption**		
Prior miscarriages	n	Rate, %	AOR (95% CI)[b]	n	Rate, %	AOR (95% CI)[b]	n	Rate, %	AOR (95% CI)[b]
No	2225	0.41	1.00	1171	0.22	1.00	1054	0.20	1.00
Yes									
1	295	0.43	1.03 (0.90–1.18)	132	0.19	0.88 (0.72–1.07)	163	0.24	1.19 (1.00–1.42)
2	64	0.56	1.30 (1.00–1.70)	37	0.32	1.45 (1.01–2.08)	27	0.24	1.17 (0.78–1.75)
>3	31	0.81	1.82 (1.25–2.66)	20	0.54	2.23 (1.37–3.62)	11	0.29	1.49 (0.82–2.71)

AOR, adjusted odds ratio; *CI*, confidence interval; *SGA*, small for gestational age.

[a] SGA defined as a live birth infant with a birthweight for gestational age more than 2 SD below the sex-specific Swedish specific growth curve. Total population is 615,130; [b] Adjustments were made for maternal age, body mass index, height, smoking, country of birth, years of formal education, in vitro fertilization, chronic hypertension, pregestational diabetes, hypothyroidism, systemic lupus erythematosis, fetal sex, and year of birth.

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remain viable but with a continued imbalance in angiogenic activity and insufficient vascular remodeling during the remaining placentation process.[4] Although we cannot exclude that the association reported is a result of residual confounding, we speculate that a causal relationship might exist between recurrent miscarriages and placental dysfunction disorders. This possible common pathogenesis might be explained by a genetic variance affecting the endometrial control of implantation or adaptation to pregnancy.[24,34,35] Genetic studies suggest that polymorphisms in the VEGF gene are associated with both recurrent miscarriages and placental dysfunction disorders.[36,37]

Placental dysfunction disorders have a recurrence risk and may predispose to each other (eg, SGA in 1 pregnancy predisposes for preeclampsia in subsequent pregnancy and vice versa).[38,39] This suggests that a failure of implantation/placentation could result in placental dysfunction disorders with different clinical features in successive pregnancies. This might be explained by an interaction between mothers susceptibility to placentation failure and fetal

TABLE 4
Risk of spontaneous preterm birth by number of prior miscarriages

	Spontaneous preterm birth[a]								
	Total (<37 wks)			Very (<32 wks)			Moderate (32-36 wks)		
Prior miscarriages	n	Rate, %	AOR[b] (95% CI)	n	Rate, %	AOR[b] (95% CI)	n	Rate, %	AOR[b] (95% CI)
No	22,738	4.40	1.00	2321	0.45	1.00	20,417	3.95	1.00
Yes									
1	2929	4.46	1.04 (1.00–1.09)	356	0.54	1.28 (1.13–1.45)	2573	3.92	1.02 (0.97–1.06)
2	552	5.05	1.18 (1.08–1.30)	87	0.80	1.84 (1.46–2.33)	465	4.26	1.11 (1.00–1.23)
≥3	232	6.45	1.50 (1.30–1.74)	44	1.22	2.60 (1.86–3.64)	188	5.22	1.38 (1.18–1.62)

AOR, adjusted odds ratio; *CI*, confidence interval.

[a] Spontaneous preterm birth defined as a birth before 37 gestational weeks with a spontaneous onset, including preterm premature rupture of the membranes. Small for gestational age births were excluded. Total population n = 596,659; [b] Adjustments were made for maternal age, body mass index, height, smoking, country of birth, years of formal education, in vitro fertilization, chronic hypertension, pregestational diabetes, hypothyroidism, systemic lupus erythematosis, fetal sex and year of birth.

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genes,[40,41] which are different in subsequent pregnancies.

We speculate that the fetal genotype might also determine the viability of a pregnancy in a mother prone to placentation failure. If the fetus has a gene variation, making it susceptible for implantation failure, this may result in a complete failure of early placentation and a subsequent miscarriage. However, if the gene combination of the fetus is more favorable, the pregnancy stays viable but with risk of later development of placental dysfunction disorder.

In women developing placental dysfunction disorders, the soluble VEGF receptor 1 (sFlt1) has been shown to be increased in the maternal circulation before the onset of symptoms.[41,42] Targeted therapy of preeclampsia aiming to remove or neutralize sFlt1 might become a reality in the future.[43,44] Recently increased sFlt1 levels in serum as well as enhanced sFLt1 expression in chorionic villus were observed in women who suffered from recurrent miscarriages.[45] One might speculate that both miscarriage and preeclampsia might be prevented by sFlt1 removal. Furthermore, women with prior recurrent miscarriages might be prone to high expression of placental sFlt1 during a viable pregnancy but with placentation failure. Therefore, these women might represent a group of patients destined to good response from sFlt1 removal in an attempt to treat or avoid later pregnancy complications such as preeclampsia, stillbirth, SGA birth, or placental abruption.

Conclusion

We report an association between increased risk of placental dysfunction disorders in primiparous women with prior miscarriages. Although the absolute risk increase was largely less than 1%, placental dysfunction disorders are serious complications of pregnancy and we advise that women with prior recurrent miscarriages should be managed as a risk group during antenatal care. Future studies are needed to evaluate the usefulness of increased surveillance during pregnancy and possibly prophylactic treatment, such as low-dose aspirin to prevent or delay the onset of placental dysfunction disorders in women with prior and especially recurrent miscarriages. ■

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